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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/736,801	KLEBL ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15,17,18,20,21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15,17,18,20,21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 12, 2007 has been entered.

Claims 2, 16, 19, 22 are cancelled. Claims 1, 18 are amended.

It is noted that in an amendment filed by Applicant December 16, 2003, claim 23 had been newly added. As such, claim 23 is included in the consideration of the claims.

Claims 1, 3-15, 17, 18, 20, 21, 23 are under consideration.

Per species election, August 24, 2005, Applicant has elected "eukaryotic cell" of claim 8. It is noted that in the past Office Actions, that the Examiner has been examining unicellular (e.g. yeast) and multicellular eukaryotic cells (e.g. mouse).

Withdrawn Rejections

35 U.S.C. § 112, 1st parag. New Matter

Applicant's arguments, see page 5 of Applicant's response, filed January 12, 2007, with respect to the rejection of claim 1, 3-17, 20, 21 as it applied to the limitation of claim 1, "wherein phenotyping is carried out by the reduction or elimination of compensating differential expression by the labeling of at least one compensating

differentially regulated gene," have been fully considered and are persuasive. It is noted that the Advisory Action of December 7, 2006 has acknowledged the withdrawal of the New Matter rejection as it applied to the claims. The rejection of claims 1, 3-17, 20, 21 has been withdrawn.

35 U.S.C. § 102

Applicant's arguments, see page 6 of Applicant's response, filed January 12, 2007, with respect to the rejection of claims 1, 3-6, 10, 16, 17 as being anticipated by Suzuki et al. have been fully considered and are persuasive. Applicant indicates that claim 1 has been amended such that there is no limitation of "the labeling of at least one compensating differentially regulated gene." The rejection of claims 1, 3-6, 10, 16, 17 has been withdrawn.

Applicant's arguments, see page 6 of Applicant's response, filed January 12, 2007, with respect to the rejection of claims 1, 3-8, 11, 14, 17, 18 as being anticipated by Rohlmann et al. have been fully considered and are persuasive. Applicant indicates that claims 1 and 17 have been amended such that the detection of the phenotype is perceptible from the outside of the animal. It is noted that Rohlmann et al. teach changes in the liver. The rejection of claims 1, 3-8, 11, 14, 17, 18 has been withdrawn.

Applicant's arguments, see page 6-7 of Applicant's response, filed January 12, 2007, with respect to the rejections of claims 1, 3, 5-9, 15, 17, 19, 20, 21 as being anticipated by Tugendreich et al. have been fully considered and are persuasive. Applicant indicates that the claims have been amended to distinguish them from

Tugendreich et al. Applicant indicates that the claims have been amended to recite that the heterologous expression of at least one protein or protein fragment by genetic modification does not produce a detectable change in the phenotype of the organism as it is perceived from the outside. It is noted that Tugendreich et al. teach that overexpression of p38 resulted in growth arrest of yeast. The rejection of claims 1, 3, 5-9, 15, 17, 19, 20, 21 has been withdrawn.

35 U.S.C. § 103(a)

Applicant's arguments, see page 7 of Applicant's response, filed January 12, 2007, with respect to the rejection of claims 20, 21 as being anticipated by Rohlmann et al. in view of Capecchi have been fully considered and are persuasive. Applicant indicates that claim 1 has been amended. As indicated above in the 102 rejection, Rohlmann et al. do not anticipate the claimed invention because Rohlmann et al. do not teach that the phenotype is on the outside of the organism. The rejection of claims 20, 21 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17, 18 are newly rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 17 and 18 encompass

humans. This is non-statutory matter. Use of the phrase, "non-human" to describe the organism would obviate the rejection.

Claims 1, 3-15, 17, 18, 20, 21, 23 are newly rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world

context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The claims are drawn to a method of making genetically modified organisms comprising the steps of a) causing heterologous expression of at least one protein or protein fragment by genetic modification of the organism, wherein the expression does not produce a detectable change of the phenotype which is perceptible from the outside of the organism, b) analyzing the modified gene expression pattern and identifying compensating differentially regulated genes, and c) phenotyping the organism following reduction or elimination of compensating differential expression which is perceptible from the outside of the organism; the organisms themselves; and the method of using the organisms in a drug screen. The specification identifies the following use for the claimed organisms and methods: the claimed organisms fill the need in the art for transgenic organisms that normally cannot be used in screens because their genetic modification does not produce any phenotype (specification, page 2, 2nd parag.).

The Examiner has considered the breadth of "eukaryotic cell" to encompass unicellular (e.g. yeast) organisms and multicellular organisms, the Examiner finds that while there is utility for the unicellular organism, yeast, there is no utility for multicellular organisms.

With regard to the asserted use of the claimed multicellular organisms in a method of drug screening, nothing in the specification provides any guidance as to what

diseases or disorders the claimed multicellular organisms have such that the claimed multicellular organisms can be used in a screen for drugs. Further, nothing in the specification teaches any specific phenotype associated with the genetic manipulations of heterologous expression of a protein or protein fragment (claim 1, step a) and the subsequent reduction or elimination of compensating differential expression genes (claim 1, step c), such that the claimed multicellular organisms could be used. Nothing in the specification teaches that any multicellular organisms were obtained according to the claimed method. In the absence of any specific teachings as to actual phenotypes or diseases associated with the claimed gene manipulations in the claimed multicellular organisms, the use of the multicellular organism in a screen is neither specific nor substantial as using the claimed multicellular organisms to further research to determine the relationship between the changes in the genome, phenotypes, and any disease is not a specific and substantial use of the claimed multicellular organisms.

Thus, for this reason, while there is utility for yeast, there is no utility for multicellular organisms.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-15, 17, 18, 20, 21, 23 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, step c, has been amended to include the phrase, "which is perceptible from the outside of the organism." Note that there is the same limitation in claim 18. Applicant indicates that support for this amendment is found on page 1, lines 33-38 (Applicant's response, page 5, under "Rejection of claims 1, 3-17, 20, and 21 under 35 U.S.C. § 112, 2nd parag."). The citation that the Applicant refers to is directed to yeast (see specification, page 1, line 30). While it is understood that yeast was provided as an example, the claims include multicellular organisms. The phrase appears to limit the phenotypes detectable in multicellular organisms as only those that are on the surface of the organism (e.g. hair and skin) and not any internal organs. Nothing in the specification indicates that this embodiment was specifically envisioned for multicellular organisms in the claimed invention. Claims 3-15, 17, 23 depend on claim 1 and are included in the rejection. Claims 20, 21, depend on claim 18 and are thus included in the rejection.

Claims 1, 3-15, 17, 18, 20, 21, 23 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are generally drawn to genetically modified organisms, the method of making the claimed organisms, and a method of using the claimed organism in a screen for drugs. With regard to the method of making the claimed organisms the specification does not provide an enabling disclosure to arrive at the claimed invention. The method

of making the claimed organisms depends on a step of analyzing the modified gene expression pattern and identifying compensating differentially regulated gene (e.g. claim 1, step b). At the time of filing, the art teaches that while microarrays have been used to determine changes in gene expression on a genome-wide level between two tissues, there are problems with using the results of microarrays reliably. King and Sinha 2001, JAMA, 286: 2280-2288, abstract, teach that some of the problems with using microarrays that would need to be addressed include the imprecise definition of "normal" in expression comparisons, the cellular and subcellular heterogeneity of the tissues being studied, the difficulty in establishing the statistically valid comparability of arrays, the logistical logjam in analysis, presentation, and archiving of the vast quantities of data generated, and the need for confirmational studies that address the functional relevance of findings. As these issues apply to the instant invention, the specification does not provide guidance as to how an artisan would address the problems associated with using microarrays, such that an artisan would arrive at the claimed invention.

First, with regard to obtaining tissue samples from multicellular organisms such that the population of cells within the tissue sample is the same has not been addressed in the specification. As such, the specification has not provided guidance as to how an artisan would discriminate changes in levels of gene expression caused by the two samples of tissue having different populations of cells from changes caused by the genetic modification in claim 1, step a.

Second, since the tissue obtained from multicellular organisms comprises a heterogenous population of cells, wherein each expresses a unique set of genes, the number of genes to look at is much larger than a homogenous population of cells, such as yeast colony. While an artisan can select genes that have large differences of expression between control and experimental tissues, the specification does not provide guidance as to how to correlate the expression to a specific cell type from the tissue. Nothing in the microarray indicates what cell type(s) correspond to the changes in gene expression. As such, it is unclear how to select cell types in which selected genes should be targeted for reduction or elimination of compensating differential expression. It is noted that reduction or elimination of compensating differential expression can also be read to encompass using transgene constructs to express a gene of interest in a cell in which the compensating differentially regulated gene is a x-fold reduction in gene expression, as compared to the wild type cell (see also claim 14). The claims can also be read that cell-specific conditional knockouts can be made. With regard to this issue, the specification provides no guidance as to how to obtain cell-specific promoters for the wide variety of cell types encompassed by the claims. Note, for example, that the art teaches that skin cells contains keratinocytes, melanocytes, Langerhans cells, Merkel cells, adipocytes, smooth muscle cells of errector pili, striated muscle cells of the panniculus carnosus, blood cells including immune system cells, and cellular elements of blood vessels, nerves, hair follicles, sebaceous glands, and sweat glands (King and Sinha, page 2282, 2nd col., under Heterogenous Cell Populations). Nothing in the specification teaches how to obtain promoters such that an artisan can reduce or

eliminate the compensating differential expression within specific cell types such that the claimed invention can be achieved.

Third, upon obtaining microarray results between two tissue samples, nothing in the specification teaches how to select for genes that are to be reduced or eliminated, as indicated in step c of claim 1. It is unclear what criteria are used to select these genes for reduction/elimination. For example, while it might be likely to disrupt the genes that have been upregulated 10-fold, it is unclear whether an artisan should disrupt genes that have been upregulated 2-fold. In addition to this issue, note that claim 1, step c, is readable such that more than one gene can be reduced or eliminated. It is unclear what single or combination of upregulated genes should be disrupted such that an artisan arrives at live organisms such that they can be used in screens for compounds, as described in claims 20 and 21 (see below for discussion that an artisan cannot necessarily predict phenotypes that result from transgenesis). Similarly, it is unclear what single or combination of genes should be avoided such that the organism obtained in step c of claim 1 has no phenotype. Because there is no guidance as to how an artisan would pick one or a specific combination of genes to reduce or eliminate in step c of claim 1, an artisan would be reduced to trial and error, in order to find organisms that exhibit a phenotype. Note for example that Table 2 in the specification teaches that 110 genes in a genetically modified yeast strain were upregulated; more than 1000 double knockouts could be generated from the list of genes provided in Table 2. This is undue experimentation.

Fourth, the art teaches that cross-hybridization between genes whose DNA sequences are similar can produce false positives (Spellman et al., 1998, Molecular Biology of the Cell, 9: 3273-3297, page 3292, 1st col., 3rd parag. under Discussion). As this issue applies to the instant invention, it is unclear which of the sequences following microarray hybridization are true positives such that an artisan can appropriately target compensating differentially regulated genes. As such, the step of using microarrays to arrive at the claimed organisms is not enabled.

Fifth, whether or not an organism has a phenotype depends on what environment was used to identify the phenotype. Similarly, whether or not an organism has a phenotype can depend on its genetic background. In the case of the environment being used to identify a phenotype, the art teaches that yeast comprising disruptions in BTN1, HSP30, and BTN2 exhibit diminished growth when grown at a particular condition, low pH (Chattopadhyay, et al., 2000, Journal of Bacteriology, 182: 6418-6423, page 6420, 1st col.). As for genetic background, Doetschmann, 1999, Laboratory Animal Sciences, 49: 137-143, page 141, 1st col., under "What is the best genetic background for knockout mice?") teaches that mice with the same gene knockout and different genetic backgrounds have widely different phenotypes. As this issue applies to the instant invention, the conditions of seeing or not seeing a phenotype in steps a) and c) of claim 1 are relative to the environment (and/or genetic background) that the organism is in and nothing in the specification provides guidance for an artisan to select particular environmental conditions and genetic backgrounds such that the method can be used to reliably obtain the organisms claimed in claims 17 and 18. For example, in

the case, of yeast, in addition to yeast growing in acidic conditions, claim 1 could encompass yeast grown at a different temperature. In the case of mice, this could encompass mice that manifest a skin condition following an allergic reaction. It is noted that while it may be implied from the specification that claim 1 may have been written in mind of using organisms of "wild type" backgrounds and at "normal" laboratory conditions, the specification has not indicated this limitation nor has the specification provided any guidance as to what a "wild type" background and "normal" laboratory conditions would be. As such, the specification does not provide guidance for an artisan to practice the claimed invention.

In addition to this issue, the art teaches that the phenotype of a knockout or transgenic mouse is unpredictable. Further, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann teaches that "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype" (Doetschmann, see page 137, col. 1, parag. 1). Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one

leaky and one null (Moens et al., 1993, Development, 119: 485-499). Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al., 1992, Nature, 359: 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al., 1987, Nature, 326: 295-298 and Jaenisch, 1988, Science, 240: 1468-1474). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans. As this issue applies to the instant invention, while the specification indicates that the claimed transgenic organisms are to be used in a method of screening for compounds, the specification does not teach that reduction or elimination of compensating differential expression of genes identified in a microarray (e.g. see claim 1, step c) results in any multicellular organism that is a model of a human disease or a disorder such that the organisms can be used to screen for compounds. Note that while the above references discuss the art in terms of knockout mice, the issue is applicable to the broad scope of any organism and to transgenic animals that overexpress a transgene construct. As such, in this aspect of the art, the

specification does not provide guidance for an artisan to arrive at the claimed multicellular organisms.

Thus, the claims are rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-17, 20, 21 remain rejected and claim 23 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed January 12, 2007 have been fully considered but they are not persuasive.

Applicant indicates that claim 1 has been amended. While the Examiner finds the amendment persuasive for claim 1, claim 1 is confusing because there is an alternate meaning for "phenotyping" in claim 11 and it is unclear what metes and bounds are encompassed by "phenotyping". Further, the Office Action of July 5, 2007, pages 5-6, indicated that the phrase, "wherein phenotyping is carried out by reducing or eliminating expression of the compensating differentially regulated gene," is contrary to the art-accepted use of the word, "phenotyping." As such, claims 1, 3-17, 20, 21, 23 are rejected.

Claim 1 uses the phrase, "perceptible from the outside," to describe a phenotype. The metes and bounds of this phrase are unclear. While the specification provides examples such as shape, size, growth, or rate of cell division (specification, page 1,

lines 33-34) and seems to imply that the phenotypes are physical attributes, it is unclear whether non-physical attributes, such as secreting a growth factor, which can be removed from the media and tested for its presence, are phenotypes encompassed by the specification.

The phrase, "modified expression," in claim 5 is confusing because it can be read two ways. In addition to the "modified expression" referring to the genetic modification of claim 1, step a), the "modified expression" could also be the expression that is reduced or eliminated in claim 1, step c).

Claim 12 is confusing. The claim reads as though the compensating differentially expressed gene is expressed at higher levels in control organisms than in those that comprise a genetic modification and that the higher gene expression levels in the control organism are reduced or eliminated. It is unclear why an artisan would reduce gene expression in the control organism.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 8-11, 17, 18, 20, 21, 23 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423.

Chattopadhyay et al. teach that the BTN1 gene was disrupted in yeast, S. cerevisiae ("btn1-Δ"), and that no phenotype was seen in these yeast. DNA microarray results of btn1-Δ yeast indicate that two genes, HSP30 and BTN2, were upregulated. Chattopadhyay et al. teach that yeast comprising deletions of HSP30, BTN1, and BTN2 exhibited diminished growth at low pH (Chattopadhyay et al., page 6418, 2nd col., 2nd parag., also page 6420, 1st col.).

Note that claim 5 is included because the claim can be read that either the genetic modification in claim 1, step a, is inducible or that the differentially expressed genes are inducible (see also 112, 2nd, above). All genes within a cell are driven by a promoter. Each promoter is induced to transcribe when transcription factors are bound to it.

Thus, claims 1, 3-5, 8-11, 17, 18, 20, 21, 23 are anticipated.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER